Chapter 4. Discussion

Through this evidence review, we have examined whole animal studies, whole animal isolated organ and cell studies, and isolated organ and cell culture studies to determine the effects of omega-3 fatty acids on arrhythmogenic outcomes and on myocardial cell organelles involved in cardiac electrogenesis. In this chapter, we discuss main findings from the studies and highlight study limitations and opportunities for future research. Findings from whole animal studies are discussed first, followed by whole animal isolated organ and cell studies and isolated organ and cell culture studies.

Whole Animal Studies

Based on the meta-analyses of the incidence of total deaths, ventricular tachycardia, and ventricular fibrillation in ischemia- and/or reperfusion-induced arrhythmias, we conclude that fish oil supplementation has anti-arrhythmic effects in the rat model when compared to omega-6-fatty acid supplementation. Our findings are summarized in the following table:

Table 4.1 Comparisons of fish-oil to Omega-6 supplementation

Experiment Conditions	Outcomes	Animal models	Omega-3 Arms	Doses of EPA+DHA (g/100 g)	# Comparisons [# Studies]	# Animals	Combined RR [a] (95% CI)
Ischemia reperfusion-induced arrhythmias	Incidence of total deaths	Rats	ALA oils	0.4 - 1.2	5 [2]	133	1.2 (0.51-2.6)
			Fish oils	1.1 - 3.7	7 [6]	169	0.47 [b] (0.23-0.93)
Ischemia-induced arrhythmias	Incidence of ventricular tachycardia	Rats	ALA oils	0.4 - 5.2	4 [3]	112	0.82 (0.65-1.0)
			Fish oils	2.1 - 3.7	6 [6]	136	0.49 (0.29-0.83)
Ischemia-induced arrhythmias	Incidence of ventricular fibrillation	Rats	ALA oils	1.1 - 5.2	3 [2]	76	0.95 (0.56-1.6)
			Fish oils	2.1 - 3.7	5 [5]	100	0.21 (0.07-0.63)
Reperfusion-induced arrhythmias	Incidence of ventricular tachycardia	Rats	ALA oils	0.4 - 1.2	5 [2]	125	1.1 (0.73-1.6)
			Fish oils	2.6 - 3.7	6 [5]	132	0.68 (0.50-0.91)
Reperfusion-induced arrhythmias	Incidence of ventricular fibrillation	Rats	ALA oils	0.4 - 5.2	6 [3]	144	0.84 (0.52-1.3)
			Fish oils	1.2 - 3.7	8 [7]	168	0.44 (0.25-0.79)

[a] Random-effect model
[b] The significantly reduced risk ration of deaths was due to a single study. After removing the study, the combined risk ratio of deaths became 0.64 (0.19-2.1)
g= grams

Fish oil supplementation in rats showed significant protective effects for ischemia- and reperfusion-induced arrhythmias by reducing the incidence of ventricular tachycardia and fibrillation. The anti-arrhythmic effects seemed stronger in ischemia-induced arrhythmias than in reperfusion-induced arrhythmias. No beneficial effects related to ischemia- and/or reperfusion-induced arrhythmias were found for alpha linolenic acid (ALA 18:3 n-3) supplementation in the rat model when compared to omega-6-fatty acid supplementation (Table 4-1). Results were consistent in the 2 studies directly comparing the anti-arrhythmic effects of ALA oils to fish oils. The incidence of total deaths, ventricular tachycardia, and ventricular fibrillation were lower in rats fed fish oil than in rats fed soybean or linseed oils (Table 3-11).

In monkey models, fish oil supplementation was found to prevent deaths in ischemia- and isoproterenol-induced arrhythmias in one study (Table 3-4). In addition, 3 studies examined ventricular fibrillation threshold and the incidence of ventricular fibrillation in induced arrhythmias. No anti-arrhythmic effects were seen in normal and ischemic conditions. There was a non-significant reduction in the incidence of ventricular fibrillation, and an increase in ventricular fibrillation threshold, in isoproterenol-induced arrhythmias among monkeys fed fish oils compared to monkeys fed sunflower seed oil (Table 3-9).

One study compared hypertensive rats fed EPA, DHA, or a mixture of EPA plus DHA, to rats fed monounsaturated fatty acid. This study showed a significantly reduced incidence of ventricular fibrillation in rats fed DHA or EPA plus DHA, but no significant reduction in rats fed EPA alone [29].

In contrast to studies of rats fed saturated fatty acids, 5 studies showed consistent protective effects on ischemia- and/or reperfusion- induced arrhythmias in rats, rabbits or pigs fed fish oils, although again the results were not statistically significant for most comparisons (Table 3-12 to Table 3-15). Similar results were found in 4 studies that compared dogs fed fish oil or EPA esters to no treatment controls (Table 3-16 to Table 3-17).

Summarizing the results from studies that compared pre-fed fish oil to pre-fed omega-6 fatty acids, monounsaturated fatty acids, saturated fatty acids, or no treatment controls across various species (rats, monkeys, dogs, rabbits, and pigs), we conclude that fish oil supplementation might have anti-arrhythmic effects when compared to omega-6 or monounsaturated fatty-acid supplementation. The anti-arrhythmic effects were apparent when animals fed fish oil were compared with those fed saturated fatty acids or with no treatment controls. In most of the studies that showed a non-significant reduction in the incidence of death, ventricular tachycardia, and ventricular fibrillation, the lack of significance was likely due to lack of statistical power. Only one study [35] reached the minimum group size to detect a 50% reduction in arrhythmic effects, as shown in Table 4.2:

Table 4.2 Minimum group size to detect a 50% reduction in ventricular fibrillation

Control group incidence in ventricular fibrillation	Group size* (N)
90	14
80	20
70	28
60	40
50	73
40	100

* Assuming two equal groups, a power of 80% to show the arbitrarily selected "physiologically" significant effect at P=.05 Adapted from Riemersma et al. [102].

TABLE 4.3 Areas for future research: Whole animal and isolated organ and cell culture studies

Outcome Variable	# of Studies Identified	Fatty Acid Tested				Results[a]		
		FO	EPA	DHA	ALA	NC	I	D
Contractile and Arrhythmogenic Parameters								
Heart Rate	4	x	x	x	-	x	-	x
Contraction Rate	4	x	-	-	-	x	x	x
Ionotropic Parameters	2	x	-	-	-	x	-	x
Cardiac Work	1	-	-	-	x	x	-	-
Basoelectromechanical Parameters								
Developed or Resting Tension	1	x	-	-	-	x	-	-
Other parameters [b]	2	x	-	-	-	x	-	x
Ion Pumps and Ion Movement								
Pump Activity	8	x	x	x	-	x	x	x
Cytosolic Calcium Influx	2	x	-	-	-	x	x	-
Cytosolic Calcium Efflux	1	x	-	-	-	x	-	-
Cytosolic Calcium Content	3	x	-	-	-	x	-	x
Sarcoplasmic Reticulum Calcium Content	3	x	x	x	x	x	-	x
Sarcoplasmic Reticulum Calcium Uptake	2	x	-	-	-	-	-	x
Sarcoplasmic Reticulum Calcium Release	0	-	-	-	-	-	-	-
Sarcoplasmic Reticulum Calcium Exchanger	1	x	-	-	-	-	x	-
Ion Currents								
Sodium Current	1	x	-	-	-	x	-	-
Transient Outward Potassium Current	1	x	-	-	-	x	-	-
Voltage Dependent L-Type Calcium Current	1	x	-	-	-	x	-	-
Delayed Rectifier Potassium Current	0	-	-	-	-	-	-	-
Inward Rectifier Potassium Current	0	-	-	-	-	-	-	-
Ultra Rapid Potassium Current	0	-	-	-	-	-	-	-
Ion Channels								
Binding to the Calcium Channel	2	x	-	-	-	x	-	x

[a] NC=no change; D=decrease; I=increase

[b] VERP (Left ventricular effective refractory period), ARP (Functional refractory period of the atrium), RRP (Relative refractory period), QRS (Ventricular conductance time), QT, MAP (monophasic action potential duration)

'-' indicates no studies; 'x' indicates at least one study

Note: This table does not include results from studies that compared young versus aged animals or different doses of omega-3 fatty acids.

Table 4.4 Areas for future research: Isolated organ and cell culture studies

Outcome Variable	# of Studies Identified	Fatty Acid Tested				Results[a]		
		FO/ Combo	EPA	DHA	ALA	NC	I	D
Contractile and Arrhythmogenic Parameters								
Spontaneous or Induced Arrhythmia	8	-	x	x	-	-	-	x
Contractility	18	x	x	x	x	x	-	x
Ionotropic Parameters	3	-	x	x	-	x	x	-
Other Contractility Parameters*	7	x	x	x	-	x	-	-
Basoelectromechanical Parameters								
Action Potential	6	x	x	x	-	x	x	x
Action Potential Amplitude	7	-	x	x	-	x	x	x
Action Potential Duration at 40% Depolarization	4	x	x	-	-	x	x	x
Action Potential Duration at 80% Depolarization	6	x	x	x	-	x	x	x
Maximum Rate of Depolarization	5	x	x	-	-	x	x	x
Maximum Diastolic Potential	3	x	x	-	-	x	-	-
Overshoot Potential	4	x	x	-	-	x	x	x
Other #	1	-	-	-	x	x	-	-
Ion Pumps and Ion Movement								
Pump Activity	1	-	x	-	-	x	-	-
Cytosolic Calcium Influx	3	-	x	x	-	x	-	x
Cytosolic Calcium Efflux	1	-	x	x	-	x	-	-
Cytosolic Calcium Content	7	-	x	x	-	x	x	x
Sarcoplasmic Reticulum Calcium Content	1	-	x	x	-	-	x	-
Sarcoplasmic Reticulum Calcium Uptake	0	-	-	-	-	-	-	-
Sarcoplasmic Reticulum Calcium Release	2	-	x	x	-	-	x	x
Sodium-Calcium Exchangers	1	-	-	-	x	-	x	-
Sodium-Hydrogen Exchangers	1	-	x	x	x	x	-	x
Calcium transients	1	-	x	-	-	-	-	x
Passive SR calcium efflux	2	-	-	-	x	-	-	x
Passive sodium influx	1	-	x	x	-	x	-	-
Ion Currents								
Sodium Current	3	-	x	x	x	x	-	x
Transient Outward Potassium Current	3	-	x	x	-	-	x	x
Voltage Dependent L-Type Calcium Current	6	-	x	x	x	x	x	x
Delayed Rectifier Potassium Current	2	-	x	x	x	-	-	x
Inward Rectifier Potassium Current	4	-	x	x	x	x	-	x
Ultra Rapid Potassium Current	2	-	x	x	-	x	-	x
Ion Channels								
Sodium Channel	1	-	x	-	-	x	-	-
Cloned Kv1.5 Potassium Channel	1	-	-	x	x	x	-	x
Calcium Channel	1	-	x	-	-	x	-	-

[a] NC=no change; D=decrease; I=increase

* tC20, CD20, CD80,-Cmax, +Cmax